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NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM1170910

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APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP-ART UNIT	DATE MAILED
08/902,516	07/29/97	024	SPECTOR, L	1646 09/10/98
First Named Applicant	HOO, WILLIAM SOD			

TITLE OF INVENTION MEMBRANE-BOUND CYTOKINE COMPOSITIONS COMPRISING GM-CSF AND METHODS OF MODULATING AN IMMUNE RESPONSE USING SAME (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEES DUE	DATE DUE
1 F-IM2442	424-093.210	183	UTILITY	YES	\$660.00	12/10/98

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT.  
PROSECUTION ON THE MERITS IS CLOSED.**

**THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS  
APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.**

**HOW TO RESPOND TO THIS NOTICE:**

I. Review the SMALL ENTITY status shown above.  
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or  
B. If the status is the same, pay the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number.  
Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/902,516	07/29/97	HOO	W P-IM2442

HM11/0910

ROBERT T RAMOS  
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SAN DIEGO CA 92122

EXAMINER

SPECTOR, L

ART UNIT PAPER NUMBER

1646

DATE MAILED:

09/10/98

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

### NOTICE OF ALLOWABILITY

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

This communication is responsive to election of 7/10/98.

The allowed claim(s) is/are 1, 7-11, 13-19, 25-35.

The drawings filed on \_\_\_\_\_ are acceptable.

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All  Some\*  None of the CERTIFIED copies of the priority documents have been  
 received.  
 received in Application No. (Series Code/Serial Number) \_\_\_\_\_  
 received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

Applicant MUST submit NEW FORMAL DRAWINGS

because the originally filed drawings were declared by applicant to be informal.  
 including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. \_\_\_\_\_.  
 including changes required by the proposed drawing correction filed on \_\_\_\_\_, which has been approved by the examiner.  
 including changes required by the attached Examiner's Amendment/Comment.

Identifying Indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

#### Attachment(s)

Notice of References Cited, PTO-892  
 Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

Interview Summary, PTO-413

Examiner's Amendment/Comment

Examiner's Comment Regarding Requirement for Deposit of Biological Material

Examiner's Statement of Reasons for Allowance

Sequence Requirement A

#9/1a  
CH  
9-9-98

**Part III: Attachment to Notice of Allowability**

**SEQUENCE COMPLIANCE:**

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, 5 this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicant must comply with the sequence rules, 37 CFR 1.821 - 1.825 within the time period set forth on the attached form PTOL-37 for compliance. Büeler et al., Molecular Medicine 10 2:545 Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). In no case may an applicant extend the period for reply beyond the SIX MONTH statutory period. Direct the reply 15 to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

**EXAMINER'S AMENDMENT**

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. 20 § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Andrea Gashler on 9/8/98.

25 **TEXT OF EXAMINER'S AMENDMENT**

The title has been amended as follows:

after the word "compositions", the phrase --comprising GM-CSF-- has been inserted.

Amend claim 1 to read as follows:

1 A pharmaceutical composition, comprising a cell having a membrane bound fusion protein comprising Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) fused to a heterologous membrane attachment domain, said cell further comprising a disease-associated antigen or immunogenic epitope thereof.

5

Cancel claims 2-6.

10

In EACH of claims 7-11, at line 1 of each claim, delete "vaccine" and insert therefore  
--pharmaceutical composition --.

Cancel claim 12.

15

In EACH of claims 13-15, at line 1 of each claim, delete "vaccine" and insert therefore  
--pharmaceutical composition --. Also, in EACH of claims 13-15, at line 1, change the dependency of the claims from claim "12" to claim --1--.

20

In EACH of claims 16 and 17, at line 1 of each claim, delete "vaccine" and insert therefore  
--pharmaceutical composition --.

25

In claim 18:

- at line 1, delete "vaccine" and insert therefore --pharmaceutical composition --
- at line 1, change the dependency from "12" to --1--
- at line 3 of the claim, delete the word "operatively".

Amend claim 19 to read as follows:

*D2* --~~N~~ A method of stimulating an immune response against a disease-associated antigen, comprising administering to an individual a pharmaceutical composition comprising a cell having:  
*a2*  
(a) a disease-associated antigen or immunogenic epitope thereof; and  
(b) GM-CSF fused to a heterologous membrane attachment domain;  
5 wherein an immune response is stimulated.

Cancel claims 20-24.

10 In claim 35, at line 3, delete "operatively".

15 Cancel claims 36-46.

#### REASONS FOR ALLOWANCE

The following is an Examiner's Statement of Reasons for Allowance:

15 The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

20 Büeler et al., Molecular Medicine 2:545, disclose that coexpression of GM-CSF with one of the tumor-specific MAGE antigens significantly increased anti-tumor immunity in an antigen-specific manner (see abstract, page 545). They also, in a discussion of the prior art at page 552, disclose that vaccination of mice with GM-CSF-secreting irradiated B16 melanoma cells has previously been shown to induce anti-tumor immunity.

25 Pardoll et al., WO 98/06746, published after the priority date, disclose a method of inducing anti-tumor immunity in which melanoma cells are obtained, modified to produce an increase level of a cytokine, and then administered to a host in which it is desired to generate anti-tumor immunity. Although Pardoll et al. provide evidence that use of GM-CSF in conjunction with such cellular immunotherapy was known in the art, there is no suggestion of using *non-soluble*, or membrane bound GM-CSF, as is claimed in the instant application. See for example,

pages 11-12.

Kubo et al., U.S. Patent number 5,662,907, disclose the use of a small peptide for induction of anti-tumor immunity (see claims). At column 12, beginning at line 44, they suggest the incorporation of such peptides into antigen presenting cells, as well as coadministration with a cytokine for the purpose of enhancing the immune response. Neither GM-CSF nor membrane bound GM-CSF are disclosed.  
5

Perez et al., Cell 63:251, cited by applicants, disclose a non-secretable cell surface mutant of Tumor necrosis factor (TNF). TNF, a cytotoxic cytokine, has both soluble and non-soluble naturally occurring forms.

10 Jadus et al., Blood 87:5232, cited by applicants, disclose that transduction of glioma cells with a membrane bound isoform of M-CSF, but not the secreted isoform of M-CSF, allowed macrophages to kill the transfected cells (see abstract).

15 Fan et al., BBRC 225:1063, cited by applicants, disclose a naturally occurring membrane bound form of IL-12, and suggest that membrane bound IL-12 could directly stimulate the IL-12 receptor upon contact with T-cells (page 1066), and thus be useful in promoting cell-mediated immunity and inflammatory reactions.

Lukacs et al., J. Exp. Med. 173:343, cited by applicants, disclose the use of tumor cells expressing a 65 kD bacterial heat shock protein for induction of protection against tumors.

20 Dranoff et al., PNAS 90:3539, cited by applicants, disclose vaccination with irradiated tumor cells engineered to secrete GM-CSF to induce "potent, specific, and long-lasting anti-tumor immunity".

U.S. Patent number 5,616,477, cited by applicants, discloses fusion proteins for use in inducing an immune response, comprising GM-CSF fused to the desired antigen. The fusion proteins are soluble.

25 U.S. Patent number 5,637,483 is drawn to a method of treating a tumor comprising administering irradiated tumor cells which have been engineered to produce soluble GM-CSF, either alone or in combination with other cytokines (see claims, and col. 18, for example).

U.S. Patent number 5,759,535 is drawn to a method for treating a mammal having a tumor, comprising administering cells which have been engineered to express one or more tumor associated antigens and a cytokine, including GM-CSF (see claims, and columns 3-4).

5        Thus, the prior art, as cited herein, teaches (a) the concept of cellular immunotherapy, in which cells expressing antigens to which an immune response is desired are administered, (b) the concept of either co-administering GM-CSF with such cells or alternatively engineering the cells to express GM-CSF, and (c) cellular therapies in which the cells express membrane bound, as opposed to soluble secreted cytokines, especially IL-12. The prior art differs from the claimed  
10      invention in that there is no suggestion in the prior art that GM-CSF has a naturally occurring membrane bound form as is the case for, for example, IL-12, nor is there any suggestion in the prior art of making a membrane bound form of GM-CSF for use in such cellular therapy. This, in combination with the enablement presented in the specification, specifically the statement at page  
15      54 that the result using cells expressing the membrane bound form of GM-CSF was significantly better than the control, in which cells expressing soluble GM-CSF, establishes non-obviousness of  
the claimed compositions and methods. Although species elections were required for the cell type  
and antigen type in addition to the election of a cytokine, the Examiner has found that, upon the  
above review of the prior art, that the patentable distinctness of the claimed invention is  
predicated on the concept of expressing a membrane bound form of GM-CSF, and has  
20      accordingly agreed to allow claims encompassing non-elected species of cell and/or antigen.

Examiner Spector conducted a telephone interview on 9/8/98 with Andrea Gashler to negotiate allowable claim language. The amendment of the claims to recite 'pharmaceutical composition' as opposed to "vaccine" is made to clarify that the composition is in a pharmaceutically acceptable state, without regard to intended use. The amendment of the claims to recite 'stimulating' rather than "modulating" (claim 19) clarifies that GM-CSF is an immunostimulatory cytokine. Deletion of the word "operatively" as applied to fusion proteins was strongly suggested by the Examiner as 'operative fusion' of sequences has an accepted  
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Serial Number 08/902516  
Art Unit 1646

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meaning in the art as applied to nucleic acids, but is less clear as applied to fusion proteins; it is not clear for what the fusion protein is 'operative', nor how a fusion protein might be 'non-operative' while still comprising the recited elements.

5 Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably accompany the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

**Advisory Information:**

10 The allowed claims, 1, 7-11, 13-19 and 25-35 have been renumbered as 1-24, respectively.

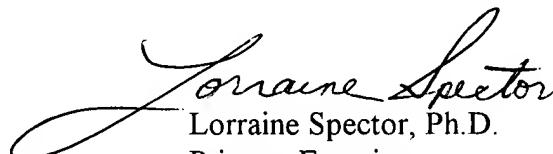
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 4:30 P.M.

15 If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ms. Lila Feisee, can be reached at (703)308-2731.

20 Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

25 Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

30 Official papers filed by fax should be directed to (703) 305-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Please advise the Examiner at the telephone number above when an informal fax is being transmitted.

  
Lorraine Spector, Ph.D.  
Primary Examiner

35

40 LMS  
902516.all  
9/9/98

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 114 FR 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of marked-up "Raw Sequence Listing."

5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

7. Other: \_\_\_\_\_

**Applicant must provide:**

An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

A statement that the content of the paper and computer readable copies are the same, and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123

For CRF submission help, call (703) 308-4212

For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.